MINI-REVIEW

Highlighting the Anti-carcinogenic Potential of an Ayurvedic Medicinal Plant *Swertia Chirata*

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Abstract

Swertia chirata **is a plant with bitter taste used since an early date in traditional medical systems of our country for treatment of varied human ailments. In Ayurveda, the plant is used as stomachic, febrifuge, antihelminthic, diuretic as well as for treatment of some types of mental disorders. Experimental revalidation of the medicinal properties of this plant along with chemical analysis of its constituents have generated interest in the medicinal value of *Swertia chirata* and is likely to open up new avenues for its multispectrum use. In view of the antioxidative, anti-inflammatory and anticarcinogenic activities reported in recent times, the plant demands a more detailed probe to determine its use in pharmaceutical industry for preparation of drugs for prevention and treatment of chronic human diseases like diabetes, cardiac problems and cancer. The aim of the present review is to draw attention of researchers in biomedical sciences and pharmaceuticals to this very important plant which has so far not received its due recognition.**

Keywords: Ayurveda medicines - *Swertia chirata* - anti-inflammatory - anticarcinogenic

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Introduction

Swertia chirata, commonly known as chirata, chirayata or kirata-tikta in Sanskrit, finds its mention in Charaka Samhita - a classical medical text of Ancient India for its multifarious therapeutic value. This plant is widely used in Ayurvedic, Unani and Siddha systems of Medicines (Williamson, 2002). Chirata is an important component of the Ayurvedic tonic "Sudarshana Churna". In traditional medicine the entire plant is used but the root is the richest source of active phytochemicals (Kirtikar and Basu, 1984). The plant has been widely used as a beneficial remedy for lung, liver, stomach and kidney ailments (Chatterjee and Pakrashi, 1995). *Swertia chirata* is a rich source of amarogentin, the bitterest compound known in nature and this phytochemical is endowed with useful medicinal properties. Researches in the recent decades have revealed hypoglycemic (Mitra et al., 1996), anti-malarial (Valecha et al., 2000), anti-inflammatory (Mandal et al., 1992), anti-oxidative (Scartezzini and Speroni, 2000) and anti-carcinogenic (Saha, 2004) actions of this plant. At the Annual Professional Conference of Diabetes UK, held in Glasgow in March 2009, researchers based on their observation announced that *Swertia Chirata* may now be considered as a potential anti-diabetic agent.

An in-depth scientific evaluation of the health promotive, protective and therapeutic effects of this plant and its phytochemicals is necessary to determine its potential importance in modern therapeutic and preventive medicine and demands a greater focus on this plant.

About the Plant

Swertia chirata belongs to the family Gentianaceae. The plant is a robust annual herb which grows upto 1.5 meters in height in the Himalayas (Kumar, 2010), usually at an altitude of 4,000-10,000 feet but it can also be grown in sub-temperate regions, as well as in a variety of soil conditions (Kirtikar and Basu, 1984; Edwards, 1993; Duke, 2002). It has leaves in opposite pair about 10 cms long, without stalks, pointed at the tip. The plant has numerous flowers, pale green in colour, tinged with purple, with long white or pink hairs. The flowering season is August to October and seeding commences in October-November. The green-yellow flowers are regular, bisexual, hypogynous and borne in leafy panicles. Fruits are small, sessile, ovate capsules. Seeds are minute and angular, have copious endosperm and a small embryo (Dutta, 1965). The plant is generally harvested around the flowering period for drug industry (CSIR, 1982).

Swertia chirata as a source of important chemical compounds

The chemical constituents of this plant have been analyzed, characterized and reviewed by several groups (Mandal and Chatterjee, 1987; Mandal et al., 1992; Chakravarty et al., 1994; Chatterjee and Pakrashi, 1995; Pant et al., 2000). The compounds isolated from *Swertia chirata* include a large number of xanthones, glycosides, alkaloids and other compounds like chiratin, ophelic

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acid, palmitic acid, oleic acid, stearic acid. The first isolated dimeric xanthone was chiratanin. Other important phytoconstituents include swerchirin, swertiamarin, swertanone, mangiferin, amarogentin, gentiopicrin and chiratol. A detailed list of compounds isolated from *Swertia chirata* is available in literature (Mandal, 1997; Joshi and Dhwan, 2005). A review of naturally occurring xanthones including gentisin, mangiferin, swerchirin is also available from an earlier article (Roberts, 1961). It needs mentioning that among the many traditionally known health protective natural compounds that have undergone scientific validation, the many phytochemicals of *Swertia chirata* has received inadequate attention till date and therefore there has been lesser exploration for determination of their medicinal properties. Fortunately in recent times these chemicals are gaining interest for the researchers. The major problem though is the non-availability of the important compounds in their pure form commercially.

Medicinal properties of *Swertia chirata* and the phytoconstituents isolated from this plant

Studies on the modulating factors of pathogenesis for many diseases, including heart diseases, diabetes and cancer, have revealed that maintenance of physiological and immunological functions of the body is the key to good health, free from chronic disorders. Many plants are used in home remedies and traditional medical practice for keeping the body functions in order. *Swertia chirata* is one such plant which is very effective for stimulation of liver function. Liver being a vital organ of the body helps in a number of ways to keep the body fit. One important role of liver is detoxification which ensures removal of toxic and damaging agents from the system thereby preventing onset of many diseased conditions.

In Ayurvedic medical practice *Swertia chirata* is one of the oldest medicinal herbs of India that was used for treatment of liver disorders (Reen et al., 2001). Anti-hepatotoxic and hepato-protective activity of *Swertia chirata* has been demonstrated by scientifically designed experimental studies (Mukherjee et al., 1997; Karan et al., 1999). Modulation of liver detoxification and protection from anti-oxidative damage were also reported (Saha and Das, 2003).

Apart from its hepato-protective role, *Swertia chirata* is also known for its anti-inflammatory, anti-mutagenic, anti-oxidative and immunomodulatory effects (Scartezzini and Speroni, 2000; Kumar et al., 2003). It is important to note in this connection that all these properties are essential for preventing cellular damage and maintenance of good health. As a crude drug 'chirata' has its use for relief of intermittent fevers, skin disease, intestinal worms, bronchial asthma and regulating bowel movement (Nandkarni, 1976; Kirtikar and Basu, 1984; Chatterjee and Pakrashi, 1995).

The array of chemical compounds isolated and identified from *Swertia chirata* account for the varied medicinal properties of this plant. Only recently the chemical compounds are being screened and validated for their actions on experimental systems *in vivo* and *in vitro*. A word of caution need to be made about the many compounds that have shown beneficial biological actions - the pure compounds are often highly toxic. Therefore extensive experimental, pre-clinical and clinical studies are required before adjudging their medicinal value and determination of the right dosages for administration as preventive and therapeutic drugs.

Anti-inflammatory action of aqueous suspension of total xanthones of *Swertia chirata* was suggested by Chowdhury et al., (1995). Further studies on the anti-inflammatory effects of orally given aqueous suspension of total xanthones as compared to the standard anti-inflammatory drugs phenylbutazole and betamethasone, revealed that chemically induced hind paw oedema in rats could be suppressed significantly (Mandal, 1997). An earlier study by the same group (Mandal et al., 1992) had reported that benzene extract of the plant containing a mixture of xanthones was effective in reducing acute, sub-acute and chronic types of inflammation both on immunological and non-immunological models. It was suggested that the plant could suppress both local and systemic manifestation of arthritis particularly the rheumatoid type.

The ethanolic extract of *Swertia chirata* was found to reduce experimentally induced gastric ulcers and prevent gastric mucosal damage by indomethacin and necrotizing agents (Rafatullah et al., 1993). A significant decrease in gastric secretion in pylorus ligated rats and inhibition of acetylcholine induced contraction of guinea pig ileum were noted, suggesting an anti-cholinergic effect of the extract.

Hypoglycemic and anti-diabetic role of *Swertia chirata* is by far the most investigated action of this plant which is well documented in literature. A 95 % ethanolic extract and four other fractions of *Swertia chirata* were tested for blood sugar lowering activity in rats. Optimum effect was noted with the hexane fraction which produced a significant fall in blood sugar without influencing liver glycogen concentration in albino rats (Sekar et al., 1987). However continuous use of the extract resulted in a rise of liver glycogen (Chandrasekar et al., 1990). The hexane fraction was identified as the xanthone 1,8dihydroxy-3,5-dimethoxyxanthone (swerchirin). It was suggested that the hypoglycemic action was through insulin releasing effect of the extract. Investigation on the mechanism whereby blood sugar was lowered by crude swerchirin isolated from the hexane fraction of *Swertia chirata* revealed that the effect was associated with marked depletion of beta-granules and pancreatic islets (Saxena et al., 1991; 1993). Further studies in vitro showed that glucose uptake and glycogen synthesis by muscle cells were significantly enhanced by serum of swerchirin treated rats; insulin release from isolated islets was also stimulated. The investigators were therefore of the opinion that swerchirin lowers blood sugar level by stimulation of insulin release from islets of Langerhans. A comparative and detailed study was undertaken on the hypoglycemic effect of three structurally unrelated compounds tolbutamide, centpiperalone and swerchirin containing fraction from *Swertia chirata* (Saxena et al., 1996). It was shown that the crude natural product produced better

effect than tolbutamide which is a dug in use (Bajpai et al., 1991). Mangiferin which is present in many plants including *Swertia chirata* may also be responsible for the hypoglycemic action of these plant extracts (Miura et al., 2001). Mangiferin was also shown to protect from oxidative damage by inducing a compensatory increase in anti-oxidant defense mechanism (Muruganandan et al., 2002) and has immuno-modulaory action.

While traditional medicines have recommended the use of *Swertia chirata* as a liver tonic, many scientific researches have provided evidences for the anti-oxidative and hepato-protective role of this bitter plant. An extensive review on the anti-oxidant activity of some traditional medicinal plants which included *Swertia chirata* is available in literature (Scartezzini and Speroni, 2000). The plants described were reported to contain anti-oxid principles that can explain and justify their use in traditional medicine in the past and present. Methanolic extracts of *Swertia chirata* is reported to possess super-oxide scavenging property (Khanom et al., 2000). Increased lipid peroxidation resulting from oxidative damage was found to be prevented by crude and pure (amarogentin rich) extract of *Swertia chirata* (Saha and Das, 2003; Saha, 2004). Hepatoprotective effect of the non-bitter components in the methanol extract was shown during paracetamol and galactosamine induced hepatotoxicity models (Karan et al., 1999). Since the two hepatotoxins used had different mechanisms of inducing toxicity, broad and non-specific protection by the extract was suggested. Protection from carbon tetrachloride induced liver damage was also noted as assessed by histopathological and biochemical parameters (Mukherjee et al., 1997).

Antihelminthic activity of aqueous and methanolic extracts of *Swertia chirata* reported by many (Iqbal et al., 2006) may be accounted for by presence of amarogentin as well as other secoiridoid glycosides like amaroswerin and sweroside.

The leishmanicidal action of amarogentin reported (Singha et al., 1992; Medda et al., 1999) was shown to be by inhibition of topoisomerase I from *Leishmania donovani* (Ray et al., 1996).

The anti-inflammatory and immunomodulatory role of amarogentin and mangiferin was considered to be through maintenance of pro-inflammatory and anti-inflammatory cytokine balance by these compounds (Nandkarni, 1976).

Anti-carcinogenic and Anti-tumour activities of *Swertia chirata*

The anticarcinogenic potential of *Swertia chirata* had remained unexplored until Das and her group took up the investigation for the first time at the department of Cancer Chemoprevention at Chittaranjan National Cancer Institute, Kolkata in collaboration with the Ayurvedic research institute in Kolkata . The aqueous and amarogentin rich crude extract of the plant was first studied and reported to have anti-carcinogenic activity on a DMBA induced mouse skin carcinogenesis model (Saha and Das, 2003; Saha et al., 2004). The action was considered to be effected by modulation of liver detoxification and reduced lipid peroxidation in DMBA exposed animals. This resulted in significant delay and reduction of papilloma formation (a pre-malignant skin outgrowth) as well as lowered the incidence of papilloma. The amarogentin rich fraction was shown to inhibit cell proliferation and enhance apoptosis, which are major physiological processes regulating tumour formation, growth and spread. The same group was also the first to observe that amarogentin could reduce hyperproliferation by downregulation of COX II protein expression which plays an important role in inflammatory reactions and cell proliferation. Up regulation of apoptosis, a process which normally eliminates undesirable cells from the system, was also noted (Saha et al., 2006). This study is now being extended to other experimental carcinogenesis models and in vitro tumour cell lines to elucidate the molecular mechanism of action of amarogentin. Studies undertaken so far on a liver model in mice have revealed that this bitter compound can restrict progression of preneoplastic lesions in liver and influence oncogene regulation (unpublished data) That *Swertia chirata* had a protective effect on liver damage induced by carbon tetrachloride, assessed by histopathological and biochemical parameters, has already been reported (Iqbal et al., 2006). Investigation is continuing to see whether influence of active liver carcinogens can be reduced by the plant extract and some of its compounds. A mouse liver carcinogenesis model was developed by using a tobacco related carcinogen N-nitrosodiethyl amine (NDEA) as a carcinogen after inducing liver damage by CCl4. This model has been histopathologically characterized and pre-cancer stages identified so as to use this model for understanding the chemopreventive and chemotherapeutic efficacy of amarogentin. Administration of amarogentine was done before initiation of carcinogenesis and during different stages of the process. Mice from different experimental groups were sacrificed at different time points following the first carcinogen application. While hepatocellular carcinoma developed in the control group after a period of time in the carcinogen exposed group, the progress of cellular changes were restricted to only mild or moderate dysplastic changes at the same time point in the groups which received preventive intervention with amarogentin (unpublished data). This is an important observation in view of the fact that Swertia chirata is recommended in traditional Ayurvedic treatment in India for maintenance of liver health as well as in treatment of various liver disorders. Our experimental studies also revealed that amarogentin treatment could reduce carcinogen induced cellular proliferation and increase apoptosis in liver lesions.

Amarogentin was found to have cytotoxic action on tumour cell lines in vitro, indicating it could be a candidate anti-cancer agent too. A recent report (Verma et al., 2008) on antiviral activity of *Swertia chirata* against herpes simplex viruses has generated further impetus to this aspect and have raised hope for a possible action of this plant extracts against cancer associated viruses particularly Human papilloma viruses.

In conclusion, plants are store houses of 'nutraceuticals' and abundant in phytochemicals which are produced by

them for their own vital functions or are produced as metabolic by products. Interestingly, these same plant products have been found to have important roles in maintenance of human health as well as prevention and treatment of many diseases.

Among the many others, *Swertia chirata* demand special attention for its varied role in human health. Unfortunately, in spite of its traditional use in our country, the plant and its chemical components have not been fully investigated to scientifically confirm earlier beliefs and reveal newer medicinal properties and to focus on their potential pharmaceutical application. The present review is therefore an attempt to throw light on the many useful medicinal properties of the plant and encourage exploitation of the same for human benefit, especially for cancer prevention. The biological action of most of the chemical components of this important medicinal plant still remains unexplored and remains to be determined. However reports available to date definitely points towards the promise *Swertia chirata* hold in therapeutic and preventive medicine.

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